Supplemental Content for: Urinary cadmium and incident heart failure: A case–cohort analysis among never-smokers in Denmark

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LIST OF SUPPLEMENTAL CONTENT

eAppendix:

More details on the Danish Diet Cancer and Health Cohort and case ascertainment

At enrollment, participants completed questionnaires to assess smoking habits, socioeconomic characteristics, diet, and physical activity. Trained research personnel also collected anthropometric measurements and urine samples. For this analysis, we excluded participants with prevalent cancer at baseline (n=581), those who did not provide a urine sample (n=390) or for whom a urine sample was not available in the biobank (n=772), and those with missing information on self-reported smoking status (n=69).

The Danish National Health Service provides free universal tax-supported health and hospital care for residents. Since 1977, any patient diagnoses in somatic hospitals have been recorded in the NPR and coded using ICD 8 (prior to 1994) or ICD 10. Beginning in 1995, diagnoses from emergency rooms and outpatient visits were also included in the NPR (1). When patients are transferred between departments, each department records a separate discharge record. Previous studies suggest the positive predictive value (PPV) of a heart failure discharge diagnosis recorded in the NPR to be at least 84% (95% CI: 81.2 – 86.6) and the PPV of incident heart failure to be 77.9% (95% CI: 74.1 – 81.6) (2,3).

Analytical chemistry methods for quantification of urinary cadmium, creatinine, osmolality, and cotinine

Within 2 hours of collection, a laboratory technician aliquoted urine samples and stored them in the biobank at -150°C. The urine was never in contact with any metal equipment nor any colored plastic (dyes used to color plastic can contain Cd). Metal analyses were conducted in the Trace Metals Laboratory at RTI International, RTP, NC, USA. We used trace metals grade concentrated nitric acid (JT Baker, Phillipsburg, NJ) and a sub-boiling acid distillation unit (Milestone DuoPur, Shelton, CT) to prepare high purity HNO_3, which we screened for impurities before use. We prepared calibration standards using National Institute of Standards and Technology (NIST, Gaithersburg, MD) traceable stock standards of analytes and internal standards (bismuth, praseodymium, holmium, scandium, and yttrium) that were purchased commercially (High Purity Standards, Charleston, SC). We prepared all samples and standards using high-purity deionized water (18MΩ or better, Pure Water Solutions).

We thawed urine samples to room temperature and vortexed to mix thoroughly. A 0.50 mL aliquot of each sample was transferred to acid-washed 15-mL polypropylene tubes. We added 0.50 mL HNO_3 and 0.050 mL of concentrated HCl to each digestion vessel and heated in a graphite heating block (SCP Science, Baie d'Urfe, Quebec) at 95 °C for 30 minutes. We allowed samples to cool to room temperature and added 0.25 mL of 30% hydrogen peroxide solution (EMD Millipore, Burlington, MA). We digested the resulting mixture at 95 °C for an additional 30 minutes. We cooled the digestion tubes to room temperature, spiked with an internal standard mixture to a final concentration of 5 ng/mL, and diluted to a final volume of 5 mL with deionized water, vortexing to mix.

To quantify 19 elements, including cadmium, we used an iCAP Q ICP-MS system (Thermo Scientific, Waltham, MA) equipped with a He gas collision cell. We tuned the instrument daily to maximize sensitivity and signal stability across the mass range and to mitigate polyatomic interferences with a mixture of 10 ng/mL In, Ce, Sc, and U. We monitored multiple isotopes for most elements to account for analytical interferences (polyatomic and isobaric), such as molybdenum oxide for cadmium.

We used NIST standard reference material (SRM) 2668 – Toxic Elements in Frozen Human Urine as a quality control sample to verify method accuracy and reproducibility. Mean recovery for cadmium in NIST SRM 2668 was 99.1% with a standard deviation of 4.2% over 47 sample batches and 9 months. We reprepared and reanalyzed approximately 10% of samples as incurred samples to provide a measure of method accuracy and reproducibility. Incurred samples generally demonstrated good reproducibility with a Pearson's correlation coefficient of 0.93.

We quantified urinary creatinine colorimetrically by the Jaffe reaction with a Cayman Chemicals (Ann Arbor, MI) Creatinine Assay Kit following the manufacturer's instructions. NIST SRM 2668 has an informational value for creatinine (626 mg/L in Level 1), so it was measured as a QC sample. Recovery of the SRM generally fell within 90-110% of the informational value.

We reanalyzed ~10% of samples as incurred samples, and the incurred values generally differed from initial measurements by less than 25% for samples above the limit of detection.

We measured urinary osmolality by the freezing point depression method using a Model 3320 Micro-Osmometer by Advanced Instruments, Inc. (Norwood, MA). We measured Clinitrol Reference Solution (Advanced Instruments, certified value 290 mOsm) and 800 mOsm Renol Urine Osmolality Control solution as daily QC samples.

We used a cotinine ELISA bioassay kit by Abnova Corporation (Taipei, Taiwan) to measure urinary cotinine, an indicator of tobacco smoke exposure. We followed the manufacturer's protocol for analysis, calibrating over the range of 0-100 ng cotinine/mL urine. We analyzed calibration standards in duplicate on all plates and analyzed several replicate samples on each plate. Incurred sample reanalysis results generally fell within ±20% difference. We diluted over-range samples into the linear range with deionized water and remeasured.

Methods for Sensitivity Analyses

We conducted a series of sensitivity analyses to assess the robustness of our findings to outliers and cadmium concentrations below the LOD. First, we repeated the main analyses after assigning cadmium concentrations below the LOD the LOD/sqrt 2 instead of the quantified cadmium concentrations. Separately, we conducted additional analyses restricting the sample to participants with creatinine-standardized cadmium concentrations between the 5^{th} and 95^{th} percentiles in adjusted models.

We conducted a series of sensitivity analyses to evaluate the impact of using creatinine standardization to account for urine dilution in our analyses. We compared our results to hazard ratios from fully-adjusted models that included creatinine as a covariate. Based on methods described by O'Brien et al (2016), we also calculated a covariate adjusted creatinine-standardized cadmium ratio (4). First, we fit a linear regression model predicting log creatinine concentrations based on age, gender, physical activity level, and BMI. Next, we divided urinary cadmium concentrations by the ratio of quantified urinary creatinine concentrations to predicted creatinine concentrations. We report continuous results per interquartile range difference in the covariate adjusted creatinine-standardized cadmium ratio to facilitate comparison across different methods. We also assessed how using osmolality and osmolality standardization to account for urine dilution alters our results. We evaluated how using these creatinine or osmolality adjustment methods of accounting for urine dilution altered results from the analyses in the combined sex and sex-stratified analyses.

Finally, in additional fully-adjusted models we: 1) included incident diabetes as a covariate, 2) excluded participants with prevalent or incident diabetes prior to heart failure, and 3) adjusted for diabetes, hypertension, and hypercholesteremia and 4) removed BMI as a covariate in fully-adjusted models. Diabetes, hypertension, and hypercholesteremia are risk factors for heart failure and could be potential confounders of the association between urinary cadmium and heart failure. However, it is also plausible that these conditions could be on the causal pathway between cadmium exposure and heart failure, and therefore, statistical adjustment may result in over-adjustment (5). To further explore how other CVD outcomes may impact our main results in fully-adjusted models we also excluded participants with acute myocardial infarction (AMI) or stroke. We conducted additional analyses excluding participants with creatinine <0.03 g/L and >3 g/L (n=58).

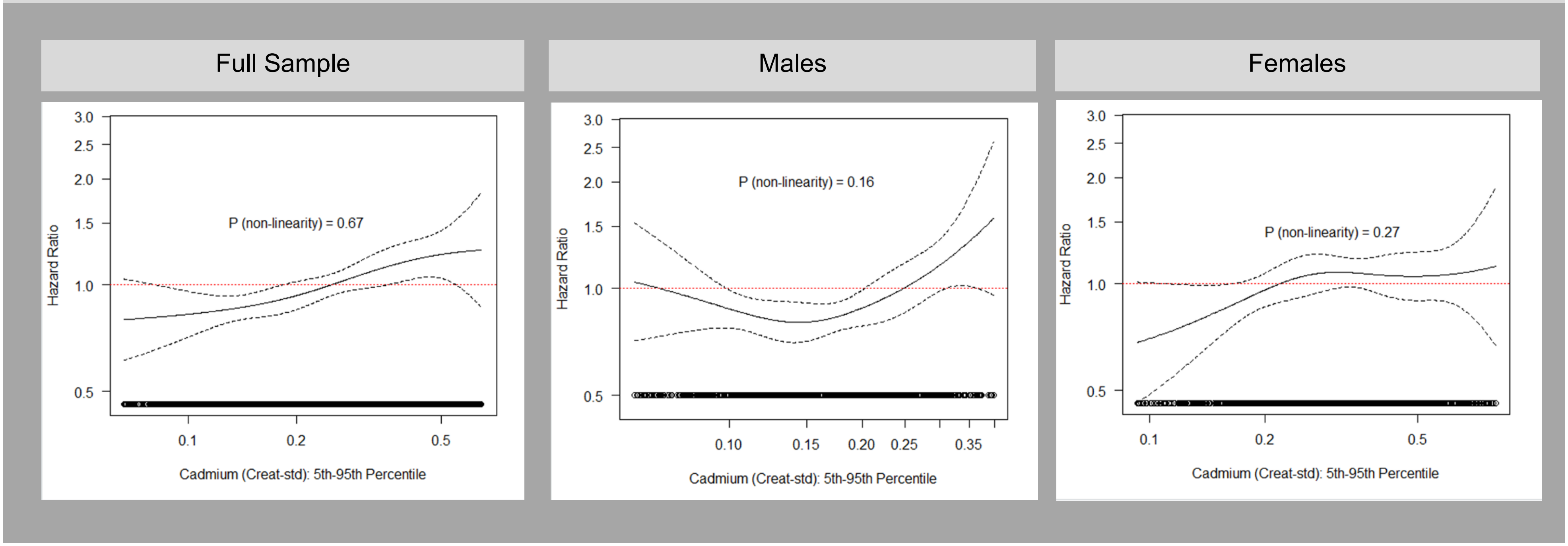
Given the possibility of confounding by tobacco smoke exposure, we conducted a series of analyses using different methods to adjust for cotinine concentrations and history of secondhand tobacco smoke exposure. We conducted analyses: 1) adjusting for cotinine as a categorical variable, 2) adjusting for cotinine and self-reported history of secondhand tobacco smoke exposure at home or work, 3) excluding participants with cotinine ≥200 ng/mL (n=46), since these participants may be current smokers (6), 4) excluding participants with cotinine ≥100 ng/mL, 4) excluding participant with cotinine ≥100 ng/mL and adjusting for cotinine concentration as well as self-reported history of secondhand tobacco smoke exposure.

Lastly, we adjusted models for concentrations of other urinary metals that are moderately correlated with urine cadmium (Spearman correlation coefficient: Pb - ρ = 0.40; As - ρ = 0.20; Sb - ρ = 0.11; Se - ρ = 0.50) (eTable 10).

eTable 1: Baseline characteristics of participants in the subcohort by cadmium quartile

	Cadmium (μg/g creatinine)			
	Quartile 1: ≤ 0.13	Quartile 2: >0.13 to 0.20	Quartile 3: >0.20 to 0.32	Quartile 4: >0.32
Total n	299	300	300	301
Median age at enrollment (25th,75th)	54 (52, 58)	56 (53, 59)	56 (52, 60)	58 (54, 62)
Sex – n (%)				
Male	228 (76)	196 (65)	133 (44)	43 (14)
Female	71 (24)	104 (35)	167 (56)	258 (86)
Education – n (%)				
Low (<8 years)	61 (20)	91 (30)	90 (30)	102 (34)
Medium (8-10 years)	94 (31)	86 (29)	68 (23)	59 (20)
High (>10 years)	144 (48)	123 (41)	142 (47)	140 (47)
Cotinine concentration – n (%)				
<= 20 ng/mL	161 (54)	168 (56)	170 (57)	191 (63)
>20 ng/ml - <50 ng/mL	99 (33)	88 (29)	80 (27)	87 (29)
>=50 ng/mL - <200ng/mL	33 (11)	38 (13)	45 (15)	18 (6)
>=200 ng/mL	6 (2)	6 (2)	5 (2)	5 (2)
BMI – n (%)				
< 25	115 (38)	118 (39)	113 (38)	133 (44)
25 to < 30	135 (45)	138 (46)	135 (45)	115 (38)
30 +	49 (16)	44 (15)	52 (17)	53 (18)
Leisure-time physical activity				
No	118 (39)	124 (41)	114 (38)	109 (36)
Yes	181 (61)	176 (59)	186 (62)	192 (64)

eFigure 1: Splines for relationship of creatinine-standardized cadmium concentration (µg/ g creatinine) with fully-adjusted hazard ratio for incident heart failure in the full sample and sex-specific strata



eTable 2: Adjusted hazard ratio (HR) for incident heart failure per interquartile range increase and quartile of urinary cadmium concentration from sensitivity analyses

U-Cd	**Model 1** Fully- adjusted HR (95% CI)	**Model 2** Fully- adjusted HR (95% CI)	**Model 3** Fully- adjusted HR (95% CI)
Continuous [a]	1.11 (1.02 – 1.21)	1.13 (1.03 – 1.23)	1.20 (1.02 – 1.41)
Quartile 1: less than or equal to 0.13	Ref	Ref	Ref
Quartile 2: greater than 0.13 to 0.20	0.93 (0.70 – 1.23)	0.91 (0.68 – 1.21)	1.02 (0.75 – 1.39)
Quartile 3: greater than 0.20 to 0.32	1.23 (0.93 – 1.63)	1.23 (0.93 – 1.62)	1.34 (0.99 – 1.83)
Quartile 4: greater than 0.32	1.29 (0.95 – 1.75)	1.27 (0.94 – 1.74)	1.33 (0.95 – 1.88)

[a] Continuous hazard ratio for an IQR=0.19 µg/g difference in creatinine standardized urinary cadmium concentration.
Adjusted models include: gender (categorical), BMI (continuous), education (categorical), and cotinine (continuous).
Continuous rate ratio for an interquartile range (IQR)=0.19 µg/g difference in creatinine standardized urinary cadmium concentration.
Interquartile range and creatinine standardized cadmium quartiles are based on concentrations among subcohort members.
Model 1: Primary results from main model
Model 2: Cadmium concentrations with values <LOD assigned the LOD/ sqrt 2
Model 3: Cadmium concentrations restricted to 5^{th} to 95^{th} percentile

eTable 3: Adjusted hazard ratio (HR) for incident heart failure per interquartile range increase and quartile of urinary cadmium concentration from sensitivity analyses using creatinine and osmolality to account for urine dilution

	Creatinine Adjusted				**Covariate Adjusted Creatine Standardization**			
U-Cd	Total	Cases (n)	Minimally-adjusted HR [a] (95% CI)	Fully-adjusted HR [b] (95% CI)	Total	Cases (n)	Minimally-adjusted HR [a] (95% CI)	Fully-adjusted HR [b] (95% CI)
Continuous [c]	2094	958	1.13 (1.02 – 1.26)	1.15 (1.02 – 1.28)	2094	958	1.17 (1.08 – 1.27)	1.13 (1.04 – 1.23)
Quartile 1	490	205	Ref	Ref	472	187	Ref	Ref
Quartile 2	514	233	1.11 (0.85 – 1.45)	1.17 (0.88 – 1.55)	508	224	1.13 (0.87 – 1.47)	1.03 (0.78 – 1.36)
Quartile 3	499	213	0.91 (0.67 – 1.22)	0.84 (0.61 – 1.16)	490	207	0.96 (0.74 – 1.25)	0.85 (0.64 – 1.13)
Quartile 4	591	307	1.38 (0.97 – 1.95)	1.44 (0.99 – 2.10)	624	340	1.51 (1.18 – 1.95)	1.27 (0.97 – 1.67)

	Osmolality Adjusted				**Osmolality Standardized**			
U-Cd	Total	Cases (n)	Minimally-adjusted HR [a] (95% CI)	Fully-adjusted HR [b] (95% CI)	Total	Cases (n)	Minimally-adjusted HR [a] (95% CI)	Fully-adjusted HR [b] (95% CI)
Continuous [c]	2090	958	1.12 (1.02 – 1.23)	1.12 (1.02 – 1.24)	2090	958	1.10 (1.02 – 1.20)	1.10 (1.01 – 1.21)
Quartile 1	490	205	Ref	Ref	499	218	Ref	Ref
Quartile 2	512	232	1.08 (0.82 – 1.43)	1.16 (0.86 – 1.56)	469	186	0.82 (0.63 – 1.07)	0.76 (0.57 – 1.02)
Quartile 3	499	213	0.86 (0.63 – 1.17)	0.82 (0.59 – 1.15)	542	257	1.04 (0.81 – 1.34)	1.02 (0.78 – 1.34)
Quartile 4	589	307	1.29 (0.92 – 1.81)	1.35 (0.94 – 1.95)	580	296	1.15 (0.89 – 1.49)	1.15 (0.87 – 1.53)

Creatinine adjusted models include creatinine as a covariate. For covariate adjusted creatinine standardization, we first fit a model for creatinine (natural log-transformed) as a function of age, gender, and physical activity. Next, we standardized urinary cadmium concentrations by calculating a ratio (U-cd/ (measured creatinine/fitted creatinine)).

Osmolality adjusted models include osmolality as a covariate. For osmolality standardization, we divided urinary cadmium concentrations by osmolality.

[a] Minimally-adjusted model includes sex.

[b] Fully-adjusted model includes: sex (categorical), BMI (continuous), education (categorical), and cotinine (continuous).

[c] Continuous Hazard ratio for an IQR difference in urinary cadmium concentration (IQR= 0.25 ng/mL) for creatinine and osmolality adjusted models. IQR difference in creatinine standardized urinary cadmium concentration (IQR=0.13 µg/g creatinine) for covariate adjusted creatinine standardization. IQR difference in osmolality standardized urinary cadmium concentration (IQR=0.36 µg Cd/ mOsM) for osmolality standardized models.

eTable 4: Adjusted hazard ratio (HR) for incident heart failure per interquartile range increase and quartile of urinary cadmium concentration from sex-stratified analyses using osmolality to account for urine dilution

	Osmolality Adjusted Fully-adjusted (95% CI)	**Osmolality Standardized** Fully-adjusted HR (95% CI)	**Creatinine Adjusted** Fully-adjusted HR (95% CI)	**Covariate Adjusted Creatine Standardization** Fully-adjusted HR (95% CI)
Male				
Continuous [a]	1.22 (1.05 – 1.41)	1.26 (1.08 – 1.45)	1.22 (1.08, 1.39)	1.48 (1.18, 1.85)
Quartile 1	Ref	Ref	Ref.	Ref.
Quartile 2	1.40 (0.91 – 2.16)	0.71 (0.49 – 1.03)	1.36 (0.91, 2.04)	0.93 (0.67, 1.28)
Quartile 3	1.03 (0.63 – 1.70)	0.97 (0.69 – 1.38)	1.01 (0.63, 1.62)	1.12 (0.79, 1.58)
Quartile 4	1.36 (0.80 – 2.30)	1.26 (0.85 – 1.86)	1.36 (0.77, 2.39)	1.99 (1.24, 3.19)
Female				
Continuous [a]	1.07 (0.95 – 1.22)	1.06 (0.95 – 1.18)	1.06 (0.96, 1.17)	1.06 (0.97, 1.17)
Quartile 1	Ref	Ref	Ref.	Ref.
Quartile 2	0.99 (0.65 – 1.51)	0.87 (0.53 – 1.41)	1.01 (0.67, 1.51)	0.93 (0.52, 1.66)
Quartile 3	0.66 (0.41 – 1.06)	1.15 (0.72 – 1.81)	0.69 (0.44, 1.08)	1.35 (0.81, 2.26)
Quartile 4	1.42 (0.84 – 2.39)	1.16 (0.75 – 1.78)	1.57 (0.94, 2.60)	1.11 (0.68, 1.82)

Osmolality adjusted models include osmolality as a covariate. For osmolality standardization, we divided urinary cadmium concentrations by osmolality. Adjusted model includes: BMI (continuous), education (categorical), and cotinine (continuous). Female model also adjusted for menopause status.
[a] Continuous Hazard ratio for an IQR difference in urinary cadmium concentration (IQR= 0.25 ng/mL) for osmolality adjusted models and IQR difference in osmolality standardized urinary cadmium concentration (IQR=0.36 μg Cd/ mOsM) for osmolality standardized models.

eTable 5: Adjusted hazard ratio (HR) for incident heart failure per interquartile range increase and quartile of creatinine standardized urinary cadmium concentration among male strata and females who are post-menopausal

U-Cd (μg/g creatinine)	**Males (n=1,041)** Fully-adjusted HR (95% CI)	**Post-menopause females only (n=668)** Fully-adjusted HR (95% CI)	**Post-menopausal and probably menopausal combined (N = 913)** Fully-adjusted HR (95% CI)
Continuous [a]	1.48 (1.18 – 1.85)	1.07 (0.96 – 1.19)	1.07 (0.97, 1.17)
Quartile 1	Ref	Ref	Ref.
Quartile 2	0.93 (0.67 – 1.28)	1.14 (0.52 – 2.50)	1.01 (0.55, 1.89)
Quartile 3	1.12 (0.79 – 1.58)	1.76 (0.85 - 3.61)	1.61 (0.92, 2.82)
Quartile 4	1.99 (1.24 – 3.19)	1.61 (0.81 – 3.19)	1.27 (0.75, 2.16)

Adjusted model includes: BMI (continuous), education (categorical), and cotinine (continuous). Interquartile range and creatinine standardized cadmium quartiles are based on concentrations among subcohort members.

[a] Continuous hazard ratio for an IQR=0.19 μg/g difference in creatinine standardized urinary cadmium concentration.

eTable 6: Adjusted hazard ratio (HR) for incident heart failure per interquartile range increase and quartile of urinary cadmium concentration from sensitivity analyses excluding participants and including different covariates

U-Cd (µg/g creatinine)	**Model 1: Fully-adjusted main results** Fully-adjusted HR (95% CI)	**Model 2: Adjusting for incident diabetes** Fully-adjusted HR (95% CI)	**Model 3: Excluding participants with diabetes** [a] Fully-adjusted HR (95% CI)	**Model 4: Excluding participants with other CVD outcomes** [b] Fully-adjusted HR (95% CI)	**Model 5: Excluding participants based on creatinine** [c] Fully-adjusted HR (95% CI)	**Model 6: Removing BMI as a covariate** Fully-adjusted HR (95% CI)
Continuous [e]	1.11 (1.02 – 1.21)	1.11 (1.02 – 1.21)	1.10 (1.00 – 1.20)	1.11 (1.01 – 1.21)	1.13 (1.03 – 1.24)	1.08 (1.00 – 1.17)
Quartile 1	Ref	Ref	Ref	Ref	Ref	Ref
Quartile 2	0.93 (0.70 – 1.23)	0.93 (0.70 – 1.24)	0.97 (0.72 – 1.32)	0.94 (0.68 – 1.31)	0.93 (0.70 – 1.25)	0.85 (0.65 – 1.11)
Quartile 3	1.23 (0.93 – 1.63)	1.21 (0.91 – 1.61)	1.26 (0.93 – 1.71)	1.26 (0.92 – 1.73)	1.26 (0.94 – 1.68)	1.11 (0.85 – 1.45)
Quartile 4	1.29 (0.95 – 1.75)	1.28 (0.94 – 1.75)	1.23 (0.88 – 1.72)	1.28 (0.90 – 1.81)	1.30 (0.95 – 1.78)	1.14 (0.85 – 1.51)

Adjusted models also include: sex (categorical), BMI (continuous), education (categorical), and cotinine (continuous).
Continuous rate ratio for an interquartile range (IQR)=0.19 µg /g difference in creatinine standardized urinary cadmium concentration. Interquartile range and creatinine standardized cadmium quartiles are based on concentrations among subcohort members: Q1= less than or equal to 0.13 µg /g; Q2= greater than 0.13 to 0.20 µg /g; Q3= greater than 0.20 to 0.32 µg /g; Q4= greater than 0.32 µg /g.

[a] Subcohort n=1078; HF cases n= 765

[b] Subcohort n=1097; HF cases n= 695

[c] Excluding participants with creatinine <0.03 g/L and >3 g/L: Subcohort n=1168; HF cases n= 928

[d] Subcohort n=1178; HF cases n= 934

[e] Continuous rate ratio for an IQR=0.19 µg/g creatinine difference in creatinine standardized urinary cadmium concentration.

eTable 7: Adjusted hazard ratio (HR) for incident heart failure per interquartile range increase and quartile of urinary cadmium concentration from sex-stratified sensitivity analyses removing BMI as a coviariate

	Male				Female			
U-Cd (µg/g creatinine)	Total (n)	Cases (n)	Fully-adjusted HR (95% CI)	Removing BMI as covariate	Total (n)	Cases (n)	Fully-adjusted HR (95% CI)	Removing BMI as covariate
Continuous [a]	1041	481	1.48 (1.18 – 1.85)	1.31 (1.05, 1.64)	1053	477	1.06 (0.97 – 1.17)	1.05 (0.96, 1.14)
Quartile 1: ≤ 0.13	385	170	Ref	Ref.	110	41	Ref	Ref.
Quartile 2: >0.13 – 0.20	313	134	0.93 (0.67 – 1.28)	0.82 (0.60, 1.12)	158	61	0.93 (0.52 – 1.66)	0.98 (0.58, 1.65)
Quartile 3: >0.20 – 0.32	240	113	1.12 (0.79 – 1.58)	0.95 (0.67, 1.32)	304	144	1.35 (0.81 – 2.26)	1.43 (0.89, 2.30)
Quartile 4: > 0.32	103	64	1.99 (1.24 – 3.19)	1.61 (1.01, 2.56)	481	231	1.11 (0.68 – 1.82)	1.14 (0.73, 1.78)

[a] Continuous HR for an IQR=0.19 µg/g difference in creatinine standardized urinary cadmium concentration.
Adjusted model includes: education (categorical-linear), and cotinine (continuous-linear). Female model also adjusted for menopause status.
P-value for sex by cadmium product term in the main fully-adjusted model: p= 0.012

eTable 8: Fully-adjusted hazard ratio (HR) for heart failure per interquartile range difference and quartile of urinary cadmium concentration from sensitivity analysis

U-Cd (μg/g creatinine)	**Model 1a: Main results minimally-adjusted model**	**Model 1b: Main results fully-adjusted models**	**Model 2a: Fully-adjusted model excluding participants** [a]	**Model 2b: Additional adjustment for covariates** [b]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Continuous [c]	1.09 (1.01 – 1.18)	1.11 (1.02 – 1.21)	1.09 (1.00 – 1.19)	1.09 (1.00, 1.19)
Quartile 1	Ref	Ref	Ref	Ref
Quartile 2	0.89 (0.69 – 1.16)	0.93 (0.70 – 1.23)	0.97 (0.72 – 1.31)	0.98 (0.71, 1.35)
Quartile 3	1.17 (0.90 – 1.52)	1.23 (0.93 – 1.63)	1.27 (0.94 – 1.70)	1.20 (0.87, 1.63)
Quartile 4	1.22 (0.92 – 1.61)	1.29 (0.95 – 1.75)	1.30 (0.94 – 1.80)	1.27 (0.91, 1.79)

Adjusted models also include: sex (categorical), BMI (continuous), education (categorical), and cotinine (continuous).

[a] Fully-adjusted model from main analyses with participants missing diabetes, hypertension, and hypercholesteremia data excluded. Subcohort n=1104; HF cases n=874

[b] Adjusted models also include diabetes, hypertension, and hypercholesteremia. Subcohort n=1104; HF cases n=874

[c] Continuous HR for an IQR=0.19 μg/g creatinine difference.

eTable 9: Adjusted hazard ratio (HR) for incident heart failure per interquartile range increase and quartile of creatinine standardized urinary cadmium concentration using different tobacco smoke exposure variables

U-Cd (µg/g creatinine)	**Model 1: Fully-adjusted main results** HR (95% CI)	**Model 2: Cotinine included as a categorical variable** [a]	**Model 2: Adjusting for self-reported secondhand smoke exposure** [b] HR (95% CI)	**Model 3: Excluding participants with cotinine ≥100** [c] HR (95% CI)	**Model 4: Excluding cotinine ≥200 ng/ml** [d] HR (95% CI)	**Model 5: Excluding participants with cotinine ≥100 and adjusting for secondhand smoke exposure** [c] HR (95% CI)
Continuous [d]	1.11 (1.02 – 1.21)	1.11 (1.02 – 1.21)	1.11 (1.02, 1.21)	1.10 (1.01, 1.20)	1.12 (1.03 – 1.22)	1.11 (1.02, 1.21)
Quartile 1	Ref	Ref	Ref.	Ref.	Ref	Ref.
Quartile 2	0.93 (0.70 – 1.23)	0.92 (0.70 – 1.23)	0.93 (0.70, 1.24)	0.98 (0.73, 1.32)	0.96 (0.72 – 1.28)	0.98 (0.74, 1.32)
Quartile 3	1.23 (0.93 – 1.63)	1.21 (0.91 – 1.61)	1.24 (0.93, 1.64)	1.16 (0.86, 1.55)	1.21 (0.91 – 1.62)	1.15 (0.86, 1.55)
Quartile 4	1.29 (0.95 – 1.75)	1.32 (0.97 – 1.80)	1.31 (0.96, 1.78)	1.23 (0.89, 1.69)	1.31 (0.96 – 1.80)	1.25 (0.91, 1.72)

All adjusted model includes: BMI (continuous), education (categorical), and cotinine (continuous).

[a] Adjusting for cotinine as a categorical variable (Table 1) instead of a continuous variable.

[b] Adjusting for self-reported history of secondhand tobacco smoke exposure at home or at work (categorical - 1: none; 2: exposure prior to age 50 years (around age of cohort enrollment) but not after; 3: both before and after age 50 years);

[c] Subcohort n=1146; HF cases=896

[d] Subcohort n=1178; HF cases=934

[d] Continuous HR for an IQR=0.19 µg/g creatinine difference.

eTable 10: Adjusted hazard ratio (HR) for incident heart failure per interquartile range increase and quartile of creatinine standardized urinary cadmium concentration from sensitivity analyses adjusting for other urinary metals

U-Cd (μg/g creatinine)	**Model 1: Fully-adjusted main results** Fully-adjusted HR (95% CI)	**Model 2: Including additional Metals as covariates** Fully-adjusted HR (95% CI)
Continuous [c]	1.11 (1.02 – 1.21)	1.10 (1.01, 1.21)
Quartile 1	Ref	Ref
Quartile 2	0.93 (0.70 – 1.23)	0.91 (0.68, 1.21)
Quartile 3	1.23 (0.93 – 1.63)	1.22 (0.92, 1.62)
Quartile 4	1.29 (0.95 – 1.75)	1.26 (0.93, 1.72)

Adjusted models include: sex (categorical), BMI (continuous), education (categorical), and cotinine (continuous).
Model 2 also includes: continuous creatinine standardized Pb, As, Sb, and Se concentrations.
Continuous rate ratio for an interquartile range (IQR)=0.19 μg /g difference in creatinine standardized urinary cadmium concentration. Interquartile range and creatinine standardized cadmium quartiles are based on concentrations among subcohort members: Q1= less than or equal to 0.13 μg /g; Q2= greater than 0.13 to 0.20 μg /g; Q3= greater than 0.20 to 0.32 μg /g; Q4= greater than 0.32 μg /g.

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